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RESEARCH ARTICLE

Quantification and Penetration Properties of p-Hydroxybenzoic Acid Derivatives

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Abstract: Parabens are widely used in many cosmetic formulations. Although there are some reports which correlate tumor growth with the use of parabens, available data on penetration through human skin is still not sufficient to fully understand their potential toxicity. The aim of this report is to investigate penetration properties of parabens through human skin. Methylparaben (MP), sodium methylparaben (NaMP), propylparaben (PP) and sodium propylparaben (NaPP) were selected as the most commonly used parabens in cosmetic formulations. In addition to UPLC method, a simple and rapid method based on dispersive liquid-liquid microextraction (DLLME) prior to capillary electrophoresis (CE) was also developed for determination of parabens. Penetration properties of parabens through full thickness of human skin were determined using Franz diffusion cell. For saturated solutions, the flux values for MP, PP, NaMP and NaPP were found to be 9.36±3.36, 4.09±1.03, 121±19 and 15.4±0.2 μg/cm^{2}h, respectively. Shampoo formulations gave a flux value of 0.545±0.271 μg/cm^{2}h for MP. The flux value of MP was found as 0.968±0.221 for hand cream, and MP and PP were 0.650±0.254 and 0.320±0.283 μg/cm^{2}h, respectively for sunscreen formulations. The flux value of MP was found as 0.677±0.273 μg/cm^{2}h for body lotion. The amount of penetrated parabens varied depending on the formulation. Hence, it was concluded that formulations should be investigated individually for paraben penetration and their possible toxic effect.

Keywords: Parabens, human skin, UPLC, capillary electrophoresis, dispersive liquid-liquid microextraction.

INTRODUCTION

p-Hydroxybenzoic acid derivatives, commonly known as parabens, are a class of chemicals that have been used as preservatives in food, pharmaceuticals and cosmetics for many years. Many pharmaceuticals and cosmetic formulations such as drug solutions, suspensions, emulsions, moisturizers, shampoos, contain parabens. Methyl- (MP), ethyl- (EP), propyl- (PP) and butylparaben (BP) are the most widely used parabens whereas isobutyl-, isopropyl-, benzylparaben and their salts are less common [1]. Until recently, parabens have been accepted as non-toxic and safe preservatives. Studies on acute, subchronic and chronic effects in animals (or in rodents) have resulted in no significant toxicity [2, 3]. Parabens were reported to be rapidly adsorbed, metabolized and excreted as *p*-hydroxybenzoic acid, *p*-hydroxyhippuric acid and *p*-hydroxybenzoyl glucuronide [2, 4]. Despite their benefits, a controversy surrounding their use has been mounting since 2004 when intact esters of five parabens were found in human breast cancer tissues at a mean concentration of 20.6 ng g^{-1} [5, 6]. Although the source of parabens could not be identified, it was suggested that dermal absorption from personal care products (PCP) such as underarm deodorants, antiperspirants and cream applied to the breast region over the long term might have an influence [6]. The estrogenic activity of parabens is of major concern [7]. Parabens are reported to mimic estrogens which are known to play an important role in the development of breast cancers and tumor mass [5]. Exposure to parabens may create a direct or indirect link between these chemicals and possible cancers or tumors. Because of these concerns, the research has been focused to elucidate this link further [8]. Although no direct evidence of any causal link between parabens and cancer has been reported, it is thought that parabens may increase the risk of any estrogen-mediated endpoints such as their influence on male reproductive tract or on breast tissue. Therefore, it was concluded that parabens are not completely safe and should be accepted as endocrine disruptors [9, 10]. The use of parabens as an antimicrobial agent in pharmaceutical formulations dates back to the mid-1920s [11]. European Cosmetic directive 76/768/EEC also

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emphasizes that the use of p-hydroxybenzoic acid to be used in cosmetic formulations should be restricted to a maximum concentration of 0.4% (as the acid) for each, and total maximum concentration should be less than 0.8% for a single ester or a mixture of esters [12, 13].

The main effect of parabens can be seen on biological membranes. They can inhibit the transport through microbial membranes and mitochondrial functions of the living cells [3]. In addition to the concerns about cancer and tumors, some experimental results have also shown that MP has the potential to create allergic contact dermatitis and UV-induced damages on skin keratinocytes [14-17]. Some disruptions of spermatogenic system have also been linked to the use of parabens, and they have been claimed to provoke spermatotoxic effects [18, 19].

Due to the increasing concerns about the safety of parabens and to the fact that almost all PCP formulations contain them [20, 21], it is important to know whether they penetrate through the skin layers or not, and the amount of the penetration [22]. Although various prediction models can be used to understand the speed and amount of paraben penetration through human skin [23-26], there is still a need to perform a series of *ex vivo* or *in vivo* penetration experiments [27]. Franz type diffusion cells have been successfully used to determine penetration of compounds through skin layers [28-32].

The penetration properties and possible toxic effects of some parabens on human skin have been investigated in the literature [13], and flux values were reported [33]. Permeability coefficients are available for pig ear skin [34], silicon membrane [35] and human epidermal skin membranes [33]; however, none of these studies were applied to the full thickness of human skin.

In this present work, a series of Franz type diffusion cell experiments was performed to understand how parabens penetrate through full thickness of human skin. Furthermore, paraben penetrations through the skin were also determined for commercial formulations available in the Turkish market. MP and PP were included in the study, and commercial formulations (i.e., hair cream, shampoo, sun screen, body lotion and hand cream) containing the two parabens were also investigated. Penetration properties of the two parabens through full thickness of human skin were determined by using an ultra-performance liquid chromatography (UPLC) method. Their concentration in cosmetic formulations was determined with capillary electrophoresis (CE) upon extraction by using dispersive liquid-liquid microextraction (DLLME), which is a very simple and rapid extraction procedure [36]. The reported methods for the determination of parabens in PCPs are mainly based on high-performance liquid chromatography (HPLC) [37] and gas chromatography (GC) [38]. However, in recent years, there has been an increasing interest in applying CE for determination of parabens [39, 40]. Finally, permeability values were calculated and compared, and the obtained values were used to discuss their toxic potentials.

MATERIALS AND METHODS

Materials

MP, sodium methylparaben (NaMP), PP and sodium propylparaben (NaPP) were donated by Abdi İbrahim Pharmaceuticals Co., Istanbul, Turkey. HPLC-grade acetonitrile (ACN), ethanol (EtOH) and methanol (MeOH) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Sodium tetraborate decahydrate ($Na_2B_4O_7.10H_2O$) was obtained from Sigma-Aldrich (Munich, Germany). Sodium chloride, chloroform (CF, log*P* 1.8), carbon tetrachloride (CTC, log*P* 3.0), sodium hydroxide and phosphoric acid were acquired from Merck (Darmstadt, Germany). 1-undecanol (1-UN, 99.0 %, log*P* 3.9) and 1-dodecanol (1-DO, 98.0 %, log*P* 4.4) were from Sigma-Aldrich (Steinheim, Germany). Paraben-containing hair conditioner, shampoo, hand cream, sun screen and body lotion were collected from local markets. Deionized (DI) water (18.2 MΩ.cm) treated with Millipore (Simplicity, 185 water purification system) Milli-Q water purification apparatus was used for all aqueous solutions.

Methods

Paraben Standard Solutions

Individual stock solutions of parabens at concentrations of 2000 μg mL^{-1} were prepared in ACN and stored at 4 ºC. Mixed standard solutions were freshly prepared at each working session from the stock solutions by proper dilutions with DI water. All solutions were degassed using a sonicator (J.P. Selecta, Barcelona, Spain) and filtered through 0.20 μm filters (Econofilters, Agilent Technologies, Darmstadt, Germany) before use.

Determination of Parabens in Cosmetic Formulations

CE Apparatus and Conditions

The experiments were performed on an HP^{3D} CE (Agilent Technologies, Waldbronn, Germany) equipped with an online UV diode-array detector (DAD) operated at a wavelength of 298 nm. Optimum wavelengths for the target analytes were determined using 'Isoabsorbance' and '3D' plots in the instrument's 'Data Analysis' software (Agilent Technologies, Waldbronn, Germany). Separations were performed using uncoated fused-silica capillaries (Agilent Technologies, USA) of 75 μm i.d. and 48.5 cm total length with effective length to the detector of 40 cm. Injection was carried out at the anodic end of the capillary, while detection was performed at the cathodic end. Separation temperature was maintained at 16 °C, and separation voltage was at 25 kV. The capillary was conditioned with a background electrolyte (BGE, 25 mM borate buffer at pH 9.2 containing 5.0% ACN, v/v); the analytes in the back-extraction solution (BES, 50 mM sodium hydroxide solution, pH 12.7) were injected for 5 s at 50 mbar. With this BGE composition, a 40-cm effective capillary length was sufficient to obtain a baseline resolution within acceptable analysis time (4 min).

New capillaries were successively flushed with DI water (10 min), 1.0 M sodium hydroxide (20 min), DI water (15 min) and finally with the BGE for 20 min. To ensure reproducibility, the capillary was flushed with the BGE (2 min) at the end of each run. The capillary was flushed for 10 min with DI water at the end of each working session, and the capillary tips were kept inside DI water till the next working session.

Sample Preparation

Dilution was adopted with the studied PCP samples (hand cream, body lotion, sunscreen, hair cream and sham-

poo) as follows: A homogenous portion of 0.5 (±0.01) g of each sample was accurately weighed in a glass test tube and mixed with DI water before being sonicated for 10 min at 60 °C, and the volume was made up to 100 mL with DI water. One milliliter of these solutions was then subjected to DLLME.

DLLME Procedure

The DLLME procedure involved transferring 1.0 mL of the sample solution into a screw-cap 15-mL conical centrifuge graduated polypropylene test tube, and the volume was made up to 7.0 mL with DI water. Next, 100 µL concentrated phosphoric acid, 200 µL chloroform and 1.0 mL ACN were added, and the mixture was vortexed for 1 min. Upon centrifugation (4000 rpm, 3 min), the dispersed fine droplets of chloroform sedimented at the bottom of the test tube and were quantitatively transferred into a 1.0-mL snaplock microtube by using a 100-µL HPLC syringe (Hamilton, USA). Finally, parabens were back-extracted into 100 µL of BES upon vortexing for 10 s and centrifugation (4000 rpm, 1 min) for direct injection into CE.

Franz Cell Diffusion Experiments

One milliliter of MP, NaMP, PP or NaPP (as saturated solutions) was added to the donor phase of Franz cell. The receptor phase was 20% (v/v) phosphate buffer solution (PBS) at pH 7.4. Full thickness human skin was used as a membrane. Skin samples were collected immediately after surgical operations at Gazi University, Faculty of Medicine, Ankara, Turkey, and stored at deep freezer until used. The full thickness of skin sample was mounted and diffusion cells were placed in a thermostated water bath; the membrane surface temperature was 32 °C, while the receptor medium was maintained at 37 °C. The cross sectional area of the skin was 1 cm^2. After each time interval, samples were taken and filtered with a 0.2 µm pore size membrane filter and replenished with a fresh solution. The amount of parabens was determined by using UPLC method, and the penetration profiles were obtained.

The steady-state permeation flux (Js) was determined from the slope of the cumulative amount of paraben permeated versus time linear graph. The lag time (T_L) showed the time required to achieve the steady-state flux, and the permeability coefficient (K_p) indicated the relation between the flux and the initial concentration of each paraben added to the donor compartment (K_p = Js/Cd).

Parabens were analyzed using the validated UPLC method. Waters Acquity UPLC system (MA, USA) equipped with a Waters 5 µm UPLC column was used. The UPLC method was adapted from the literature (41), and the details of gradient condition of UPLC method were given in Table **1**.

In the present study, the steady-state permeation flux was determined from the linear part of the amount of penetrated parabens versus time graph [34]. The permeability coefficient (P) was calculated as the ratio of the flux values and the initial concentration of parabens in the donor phase in the Franz cell compartment. Statistical analysis was performed using ANOVA/SPSS tests. A *p*-value less than 0.05 was considered significant.

RESULTS

Analytical performance of the developed CE method for commercial formulations was shown in Table **2**. The concentrations of MP and PP in the commercial formulations were determined by using CE, and the results were given in Table **3**. To examine the performance of the proposed DLLME-CE method with the PCP samples, matrix-matched calibration graphs were constructed by spiking sample solutions with appropriate amounts of mixed standard solution of the two analytes. A series of samples containing a mixture of the two parabens at five concentration levels of 0.0, 1.5, 3.0, 4.5 and 6.0 µg mL^{-1} was used. The samples were then subjected to the DLLME procedure. For each level, triplicate extractions were performed, and average peak areas were used for quantification. Regression equations, coefficients of determination (R^2), precision in terms of intraday and interday, percentage of relative standard deviation (%RSD), limits of detection (LOD), limits of quantitation (LOQ) and linear dynamic ranges (LDR) were summarized in Table **2**. The response was linear over the concentration range from their corresponding LOQs up to 6.0 µg mL^{-1} for both analytes, with R^2 higher than 0.9955. LODs were found as 0.03 and 0.22 µg mL^{-1}, and LOQs were 0.10 and 0.74 µg mL^{-1} for MP and PP, respectively. Reproducibility of the proposed method was evaluated in terms of intraday and interday precision by extracting the spiked samples at the five concentration levels of the calibration graphs for both parabens in the same day and within

Table 1. UPLC method for parabens

Time (Minutes)	Flow Rate	A%	B%
Initial	0.25	50	50
1	0.25	50	50
2	0.25	100	0
2.5	0.25	100	0
2.7	0.25	50	50
3	0.25	50	50

A: MeOH, **B:** 10% MeOH + 0.05% o-phosphoric acid + distilled water up to 100 mL.
Detection was carried out at 260 nm. Aquity UPLC BEH C18 1.7 µm 2.1x50 mm column was used.

Table 2. Analytical performance of DLLME-CE in PCP samples.

PCP	Paraben	Regression equation[a)]	R^2	RSD (%, n = 3)		LOD[b)] ($\mu g\ mL^{-1}$)	LOQ[c)] ($\mu g\ mL^{-1}$)	LDR[d)] ($\mu g\ mL^{-1}$)
				Intraday	Interday			
Hair conditioner	MP	y = 10.63(±0.26) x - 1.20(±0.79)	0.9955	2.4	3.5	0.22	0.74	0.74-6.0
Body lotion	MP	y = 10.63(±0.26) x - 1.20(±0.79)	0.9955	2.4	3.5	0.22	0.74	0.74-6.0
	PP	y = 17.05(±0.05) x - 0.24(±0.17)	0.9999	0.3	0.5	0.03	0.10	0.10-6.0
Sunscreen	MP	y = 10.63(±0.26) x - 1.20(±0.79)	0.9955	2.4	3.5	0.22	0.74	0.74-6.0
	PP	y = 17.05(±0.05) x - 0.24(±0.17)	0.9999	0.3	0.5	0.03	0.10	0.10-6.0
Shampoo	MP	y = 10.63(±0.26) x - 1.20(±0.79)	0.9955	2.4	3.5	0.22	0.74	0.74-6.0
	PP	y = 17.05(±0.05) x - 0.24(±0.17)	0.9999	0.3	0.5	0.03	0.10	0.10-6.0
Hand cream	MP	y = 10.63(±0.26) x - 1.20(±0.79)	0.9955	2.4	3.5	0.22	0.74	0.74-6.0

a) Peak area = slope(±SD[standard deviation]) × [paraben concentration ($\mu g\ mL^{-1}$)] + intercept(±SD).
b) LOD: limit of detection.
c) LOQ: limit of quantitation.
d) Linear dynamic range.

Table 3. Concentration of parabens in the PCP samples.

PCP	Concentration ($\mu g\ g^{-1}$) (±SD)	
	MP	PP
Hair conditioner	3238(±77.7)	<LOD
Body lotion	160.0(±3.8)	<LOD
Sunscreen	6378(±153.1)	1817(±5.5)
Shampoo	11960(±287.0)	<LOD
Hand cream	1300(±31.2)	<LOD

same day and within three consecutive days. An acceptable precision was obtained in all cases with %RSD values below 2.3% for intraday and 3.5% for interday experiments.

Hair conditioner was found to contain MP at 3238 $\mu g\ mL^{-1}$ (0.32%, w/w), body lotion contained MP at 160.0 $\mu g\ g^{-1}$ (0.02%, w/w), sunscreen contained MP and PP at 6378 $\mu g\ g^{-1}$ (0.64%, w/w) and 1817 $\mu g\ g^{-1}$ (0.18%, w/w), shampoo had MP at 11960 $\mu g\ g^{-1}$ (1.2%, w/w), and hand cream contained MP at 1300 $\mu g\ g^{-1}$ (0.13%, w/w) (Table **3**).

Ex-vivo transdermal permeations of parabens from saturated solutions were studied, and the permeation profiles through human skin were presented in Fig. (**1**).

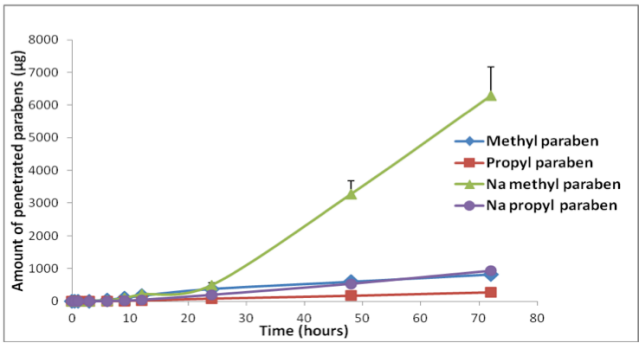

Fig. (1). Penetration of parabens (MP, PP, NaMP and NaPP) through human skin from saturated solutions (n=3, mean ±SD).

Commercial formulations (i.e., hair cream, shampoo, sun screen, body lotion and hand cream) which contained MP and MP together were also investigated in terms of the permeation properties through human skin.

The results of flux values for MP, PP, NaMP and NaPP were found as 9.36±3.36, 4.09±1.03, 121±19, and 15.4±0.2 μg/cm^{2}h, respectively for saturated solutions. The permeation parameters of saturated solutions obtained in this study were shown in Table **4**.

The flux values were found as follows: 0.545±0.271 μg/cm^{2}h for MP in shampoo, 0.968±0.221 μg/cm^{2}h for MP in hand cream, 0.650±0.254 and 0.320±0.283 μg/cm^{2}h for MP and PP in sunscreen, respectively, and 0.677±0.273 μg/cm^{2}h for MP in body lotion.

The penetration of parabens through full thickness of human skin was evaluated, and the flux values were given in Table **5**. The permeability coefficient (logK_p) was obtained by dividing the J values from Table **3** to the donor concentrations.

DISCUSSION

In this study, a CE method combined with DLLME was also developed with the aim of minimizing the consumption of organic solvents to determine parabens in commercial formulations. Effective experimental parameters on extraction efficiency which included the type and volume of extraction and disperser solvents, ionic strength, extraction/back-extraction time and volume of BES were investigated and optimized. The effect of paraben combinations on their transdermal permeation was evaluated in the literature by using pig ear skin [34], silicon membrane [35] and human epidermal skin membranes [33]. In this present study, the method was similar to the work of Caon *et al*.; however, they evaluated the effect of paraben combinations on the transdermal permeation for pig ear skin by using only Franz diffusion cell system with CE (34). Oliveira *et al*. investigated the role of the volatile solvent ethanol combined with the penetration enhancers on the efficacy of dermal delivery of MP only [33]. In the present study, such effects for full thickness of human skin we evaluated by using Franz diffusion cell system with a UPLC method.

When the permeation profiles of MP and PP were compared, MP was found to have higher penetration values through human skin, followed by PP as shown in Fig. (**1**). After 72 hours, the results revealed that the final amount of MP, PP, NaPP retained in human skin were different, which indicates substantial differences in the transport of each paraben. MP, PP and NaPP showed higher retention behavior in human skin compared to NaMP. NaMP penetration was also found to be substantially higher than that of NaPP. It was also found that the most lipophilic paraben, i.e., PP, has lower flux values. This result demonstrated that PP interacted with the human skin with a greater extent due to strong interactions with lipids. The penetration behavior of NaMP is substantially different from that of NaPP as shown in Fig. (**1**). The observed increase may be associated with the solubility of NaMP, which could be the reason for its partitioning behavior within the skin layers.

As shown in Fig. (**2**), commercial formulations containing MP represented higher penetration values compared to the PP-containing formulations. Similarly, the data from Fig. (**1**) confirmed that lipophilicity of parabens was the reason for the permeation behaviours of parabens. When the flux

Table 4. Permeation parameters of parabens from saturated solutions.

Parameter	Methyl paraben	Propyl paraben	Na methyl paraben	Na propyl paraben
J (mean ±sd)(μg/cm^{2}h)	9.36±3.36$^{(a)}$	4.09±1.03$^{(a)}$	121±19$^{(b)}$	15.4±0.15$^{(a)}$
T_L (mean±sd)(h)	17.2±11.4$^{(a, b)}$	6.14±6.28$^{(a)}$	20.2±1.05$^{(b)}$	11.8±6.84$^{(a, b)}$
logK_p (mean±sd)(cm/h)	-2.39± 0.16$^{(a)}$	-1.79± 0.11$^{(b)}$	-3.04± 0.07$^{(c)}$	-3.01± 0.01$^{(c)}$

ANOVA/SPSS tests ($p<0.05$) were carried out as appropriate (n=3). Different letters indicate significantly statistical differences among treatments. Each permeability parameter was analyzed separately. J means the steady state permeation flux. T_L means lag time and Log K_P means permeability coefficient

Table 5. Flux values of parabens from different commercial formulations, (n=3, mean ±SD).

Penetrant	Formulations	J (mean ±sd)(μg/cm^{2}h)	logK_p (mean±sd)(cm/h)
MP	Hair conditioner	1.13±0.59$^{(a)}$	-3.47±0.233$^{(a)}$
MP	Body lotion	0.677±0.273$^{(a)}$	-2.38±0.176$^{(b)}$
MP	Sun screen	0.650±0.254$^{(a)}$	-4.00±0.165$^{(c)}$
MP	Shampoo	0.545±0.271$^{(a)}$	-4.36±0.240$^{(d)}$
MP	Hand cream	0.968±0.221$^{(a)}$	-3.13±0.096$^{(e)}$
PP	Sun screen	0.320±0.283	-3.80±0.394

ANOVA/SPSS tests ($p<0.05$) were carried out as appropriate (n=3). Different letters indicate significantly statistical differences among treatments. Each permeability parameter was analyzed separately. J means the steady state permeation flux and Log K_P means permeability coefficient

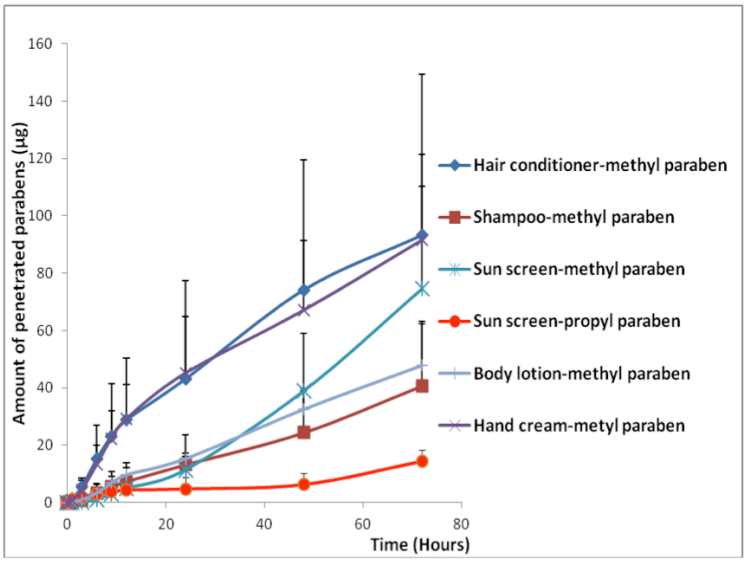

Fig. (2). Penetration of parabens (MP, PP) through human skin from different commercial formulations (n=3, mean ±SD).

values of the MP and PP were compared, MP showed higher flux values over PP. NaMP presented higher flux, followed by NaPP. As can be seen in Table **4**, different parabens were used, and it could be the reason for the discrepancies between the data.

The present study demonsrated that all flux values regarding the commercial formulations of parabens were not statistically different. On the other hand, logK_p values were found to be statistically different. The flux values and permeability coefficient values of PP were excluded from the statistical evaluation. Table **5** shows that the permeability coefficients of PP can differ according to the type of formulations. The flux values of hair conditioner and hand cream were markedly higher than those of the other formulations. When logK_p values were compared, the highest one was found for body lotion. These differences can be related to the composition of formulations and the concentration of parabens in them. The observed permeation properties of parabens were in line with the data given in the literature [34]. It was reported that lipophilicity affects the permeation properties, and different lipid contents of human skin could be the reason for obtaining a different permeation behavior of parabens [42,43]. These flux values proved that the increase in lipophilicity resulted in lower flux values. Similar results were observed when T_L (lag time) values were evaluated. An increase in the T_L values was observed when PP and NaPP were compared to MP and NaMP. The differences were statistically significant when T_L of PP was compared to that of NaMP. When the permeability coefficients were compared, the value of PP was found to be the highest one, followed by MP, NaMP and NaPP. logK_P values of MP and PP were statistically different ($p<0.05$) and were higher than those of NaMP and NaPP. MP and PP flux values were found to be lower than those obtained by Caon *et al*. and Akomeah *et al*. [34, 44]. The observed differences could be due to the use of different membranes and tissues. It is also thought that different animal species may give different results.

As shown in our results, the flux values obtained from the commercial formulations were found to be significantly low compared to saturated solutions of parabens. The formulation types and their excipients could affect the adsorptions of parabens, as reported by Caon *et al*., Dal Puzzo *et al*., and El Hussein *et al*. [34, 42, 43]. The low permeation flux values from formulations resulted in high retentions which can reduce adverse effects.

Although chemical structures of parabens are not considered to have high carcinogenic potential, parabens have been reported to be present in some breast tumors [6]. Especially MP is rapidly metabolized and excreted from the body without accumulation of parent compound or metabolites. It is recognized that the use of MP and PP in topical preparations is quite common, and using them as preservatives in cosmetic products to be applied on undamaged skin has been considered to be safe [3]. However, when applied to damaged skin, its permeability is substantially enhanced, and their penetration can reach a toxic level [45]. After extensive search in the scientific literature, it was concluded that PP shows rather low acute and chronic toxicities. Other parameters of safety assessments are also negative, and the substances (e.g., MP) are consistently negative in the case that specific data for PP is not available analogous [46]. However, our experimental results showed that penetration levels and properties of parabens completely depend on the formulations and excipients. Although all tested formulations contained parabens at allowed concentrations set by the European Cosmetic directive 76/768/EEC, they can still provide enough parabens to be penetrated through the skin. In particular, the commercial formulations of parabens are prepared to ensure safety for the topical use since high amount of parabens could enter the body. To avoid the human skin absorption and enable preservative properties of parabens, commercial formulations representing low penetrations of parabens should be prepared.

In the present study, all the results revealed that MP has higher penetration values through the human skin than PP. Penetration of NaMP was found to be substantially higher than that of NaPP. The observed difference may be related to their lipophilicity. Similar results given in the literature

proved that lipophilicity affects the permeation level, i.e., the most lipophilic paraben (i.e., PP) has a lower flux value [34, 43, 47, 48].

CONCLUSION

In this study, two sensitive and reliable analytical methods based on UPLC and CE have been developed for the determination of MP, PP, NaMP and NaPP, and skin penetrations of these parabens were successfully determined. Penetration of parabens from various formulations available in the Turkish market was also determined. It was found that the penetration of MP in hair conditioner and hand cream was higher than the penetrations in other formulations. It was also concluded that some formulations provide faster penetration opportunities for parabens, and our results may also help researchers working in this field.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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